Does Being Overweight Really Reduce Mortality?

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Does Being Overweight Really Reduce Mortality?

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Abstract

There is indisputable evidence from epidemiologic and clinical studies that being overweight and obese elevates the risk of developing debilitating and costly chronic diseases, including hypertension, hypercholesterolemia, type 2 diabetes, cardiovascular diseases (CVD), and cancer (1). Nonetheless, the relationship between body mass index (BMI) and mortality remains the subject of much debate. A recent meta-analysis concluded that compared to those of normal weight (BMI<25.0), overweight individuals (BMI 25.0–29.9) had a significantly lower mortality risk (2). Even Class 1 obesity (BMI 30–34.9) was associated with marginally reduced mortality. In this Perspective, we discuss why this finding is likely to be an artifact of methodological limitations and what the clinical and public health implications may be.

Keywords

Obesity; overweight; mortality; reverse causation; chronic disease; body mass index

Methodological Biases in BMI and Mortality Analysis

Although total mortality is a straightforward endpoint, epidemiologic studies of body weight and mortality are particularly prone to two major sources of bias: reverse causation and confounding by smoking (3). Reverse causation is a concern when a lower body weight is the result of an underlying illness through the disease process itself, or through a conscious effort to lose weight motivated by a clinical diagnosis. Furthermore, this potential for bias increases with older age as chronic diseases accumulate. While exclusion of participants with known disease at baseline addresses much of this bias, many chronic conditions such as pulmonary and neurodegenerative diseases remain undiagnosed for years. There is no perfect solution to deal with this problem; however, excluding deaths occurring early in follow-up can also help to reduce reverse causation.

Confounding by smoking is another major threat to BMI-mortality analysis. Differences in intensity, inhalation, frequency, and duration, coupled with smoking's very strong association with mortality risk and association with lower body weight, make simply adjusting for smoking status in a statistical model an inadequate control for its confounding. To avoid this residual bias, it is now standard practice to conduct the analyses restricted to never smokers.

These methodological biases are exacerbated when a wide comparison group (BMI 18.5 to <25) is used because this group (especially the lower end of normal weight) contains not

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only those who are lean and active, but also heavy smokers, individuals with chronic diseases, and frail elderly individuals. In populations undergoing nutritional transitions (e.g., China and India), low BMI groups also include those affected by malnutrition and infectious diseases. Comparing overweight and obese groups to this heterogeneous stratum seriously underestimates their relative mortality risk.

As mentioned above, it is critical to conduct stratified analysis by smoking status. For example, in the Prospective Studies Collaboration (Figure 1), there was an approximately linear relationship among the never smokers, while a nonlinear J-shaped relationship persisted among smokers (4). The lack of subgroup analyses among non-smokers or individuals <65 years old casts doubt on the validity of conclusions derived from the meta-analysis by Flegal et al.

What Have Other Studies Shown?

Flegal et al. emphasize that a strength of their meta-analysis is their use of standard BMI categories. While the separate sensitivity analyses included EXTRAPOLATED ESTIMATES FROM SEVERAL large studies, the main analysis excluded MANY LARGE COHORTS OR CONSORTIA (Table 1) (4–9) which had sufficient statistical power to allow for the analysis of finer BMI categories and assessment or non-linear associations. Including only studies with broad BMI cut-points therefore resulted in an over-representation of smaller clinical populations, high-risk patients with particular illnesses or living in metabolic wards, and the elderly. In the excluded studies (>6 million individuals), the lowest mortality was frequently observed among those with BMI 22.5–25, especially among healthy nonsmokers (Table 1). These studies provide convincing evidence that optimal BMI for longevity is below a BMI of 25.

Generalizability vs. Validity

It has been argued that exclusion of participants with CVD and cancer at baseline produce misleading associations between BMI and mortality because the resulting sample would not reflect the US population. However, these exclusions are necessary to obtain valid estimates of mortality risk. For example, in a study of cigarette smoking and mortality, if patients with CVD and cancer at baseline were included, the effects of smoking in the general population would be seriously underestimated, as the “nonsmoking” patients would include ex-smokers who quit due to illness but remain at an elevated risk of early death. Clearly, validity is the overriding objective of epidemiologic studies, because non-valid results cannot be generalized to any populations, including its own participants. From a public health perspective, our ultimate goal is to identify the optimal BMI to reduce risk of chronic disease and premature mortality, rather than pure statistical prediction.

Obesity Paradox

Obesity has been associated with improved survival in patients with existing chronic diseases, including congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), chronic kidney disease, and other wasting conditions —a phenomenon referred to as “reverse epidemiology” or the “obesity paradox” (1). In these ill patients, other cardiovascular risk factors (e.g., blood pressure and serum cholesterol) are also inversely associated with mortality. One hypothesis proposed to explain these phenomena is that obese patients benefit from a metabolic or nutritional reserve, improving their survival in conditions of illness; however, a more plausible explanation for the “reverse epidemiology” is the presence of methodological problems, especially reverse causation and survival bias. Clinically, weight gain is not a desirable recommendation for most chronically ill patients, who are often already overweight or obese to begin with.

Clinical and Public Health Implications

Flegal et al. suggest that their meta-analysis may "help to inform decision making in the clinical setting." However, their conclusion suggesting a reduced mortality among the overweight and Class I obese patients is flawed and misleading. While not all overweight and obese adults presently display signs of metabolic dysfunction or disease, this state deemed "metabolically healthy obesity" has been shown to be only transitory for most (10). Maintaining a healthy weight through diet and physical activity should remain the cornerstone to prevention and treatment of chronic diseases, and is critical for reducing skyrocketing health care costs. In addition to monitoring body weight, monitoring changes in waist circumference and the amount of weight gain since young adulthood is also important for enjoying a long and healthy life.

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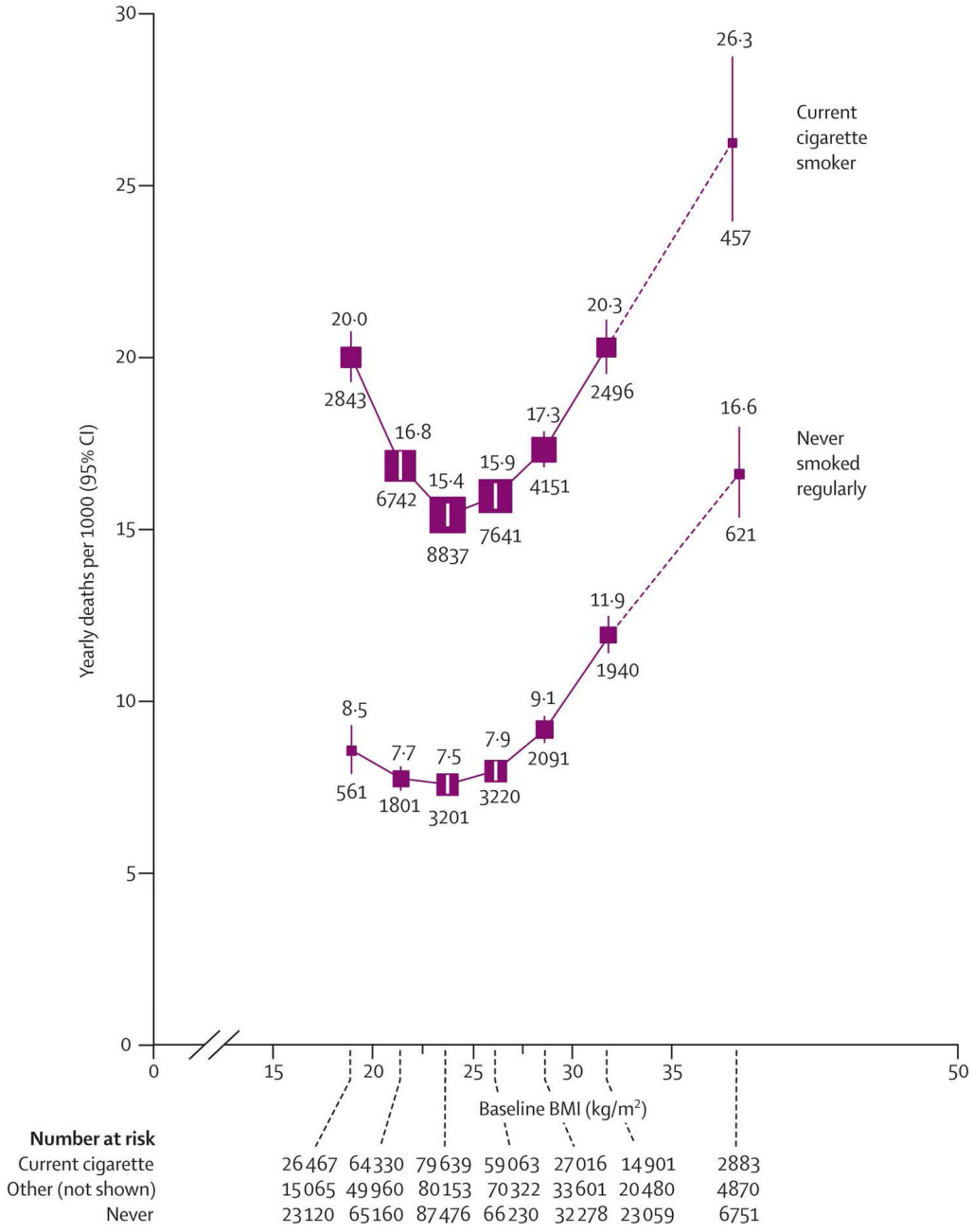

Figure 1.

All-cause mortality at ages 35–79 years versus BMI in the range 15–50 kg/m^2, by smoking status (excluding the first 5 years of follow-up), Reproduced with permission from Prospective Studies Collaboration (4)

"Relative risks at ages 35–79 years, adjusted for age at risk, sex, and study, were multiplied by a common factor (ie, floated) so that the mean for all participants (including ex-smokers and anyone with missing smoking data) matches the European rate at ages 35–79 years in 2000. Results for ex-smokers and those with missing smoking data not shown (but are, taken together, only slightly above those for never smokers). Note that many smokers were at only limited risk, since they had not smoked many cigarettes during early adult life, or had stopped shortly after the baseline survey. Risk is indicated on an additive rather than

multiplicative scale. The estimates for 35–50 kg/m^2 are based on limited data, so lines connecting to those estimates are dashed. Floated mortality rates shown above each square and numbers of deaths below. Area of square is inversely proportional to the variance of the log risk. Boundaries of BMI groups are indicated by tick marks. 95% CIs for floated rates reflect uncertainty in the log risk for each single rate." (Whitlock G, Lewington S, Sherliker P, et al. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet 2009;373:1083–96. Figure 6.

Table 1

Summary of findings from publications on BMI and mortality among the total population and healthy never smokers, omitted from the meta-analysis by Flegal, et al (2)

Study	Total Subjects	Total Deaths	Mean Age	Mean Follow-Up	Ref BMI	All-Cause Mortality RR (95% CI) by BMI Category *Total Population*			All-Cause Mortality RR (95% CI) by BMI Category *Healthy Never Smokers*		
						Overweight I	**Overweight II**	**Obese**	**Overweight I**	**Overweight II**	**Obese**
National Cancer Institute (NCI) cohort consortium (5)	1,462,958	160,087	58y *	10y *	22.5 to 24.9	BMI: 25–27.4 W: 1.05 (1.03–1.07) M: 0.97 (0.96–0.99)	BMI: 27.5–29.9 W: 1.14 (1.11–1.17) M: 1.05 (1.02–1.07)	BMI: 30–34.9 W: 1.31 (1.28–1.34) M: 1.18 (1.15–1.21)	BMI: 25–27.4 W: 1.09 (1.05–1.14) M: 1.06 (1.01–1.12)	BMI: 27.5–29.9 W: 1.19 (1.14–1.24) M: 1.21 (1.14–1.28)	BMI: 30–34.9 W: 1.44 (1.38–1.50) M: 1.44 (1.35–1.53)
Asia cohort consortium (6)	1,141,609	120,758	53.9y	9.2y	22.6 to 25.0	BMI: 25.1–27.5 E. Asian: 0.98 (0.95–1.01) S. Asian: 0.98 (0.84–1.13)	BMI: 27.6–30.0 E. Asian: 1.07 (1.02–1.12) S. Asian: 0.94 (0.77–1.16)	BMI: 30.1–32.5 E. Asians: 1.20 (1.10–1.32) S. Asians: 1.03 (0.77–1.39)	BMI: 25.1–27.5 E. Asians: 1.00 (0.95–1.06) S. Asians: 0.97 (0.82–1.16)	BMI: 27.6–30.0 E. Asians: 1.11 (1.04–1.20) S. Asians: 0.94 (0.74–1.19)	BMI: 30.1–32.5 E. Asians: 1.27 (1.12–1.43) S. Asians: 1.01 (0.73–1.41)
Prospective Studies Collaboration (4)	894,576	66,552	46y	13y	NA	BMI: 15–25† W: 0.80 (0.75–0.80) M: 0.79 (0.76–0.82) Mortality lowest at BMI~22.5–25		BMI: 25–50† W: 1.26 (1.23–1.30) M: 1.32 (1.29–1.36)	BMI: 15–25† W: 0.87 (0.78–0.97) M: 0.87 (0.78–0.97) Mortality lowest at BMI~22.5–25		BMI: 25–50† W: 1.27 (1.22–1.32) M: 1.44 (1.36–1.53)
Cancer Prevention Study II (7)	1,046,154	201,622	57y	14y	23.5 to 24.9	-	-	-	BMI: 25–26.4 White W: 1.07 (1.01–1.13) White M: 1.04 (0.98–1.10) Black W: 0.90 (0.71–1.15) Black M: 1.20 (0.86–1.68)	BMI: 26.5–27.9 White W: 1.10 (1.04–1.17) White M: 1.09 (1.02–1.16) Black W: 0.97 (0.77–1.22) Black M: 1.13 (0.81–1.59)	BMI: 30.0–31.9 White W: 1.30 (1.22–1.39) White M: 1.32

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						Overweight I	Overweight II	Obese	Overweight I	Overweight II	Obese
											(1.21–1.45) Black W: 1.17 (0.92–1.48) Black M: 1.29 (0.87–1.90)
European Prospective Investigation into Cancer and Nutrition (EPIC) (8)	359,387	14,723	51.5y	9.7y	23.5 to 24.9	BMI: 25–26.4 W: 1.01 (0.92–1.11) M: 0.91 (0.84–0.99)	BMI: 26.5–27.9 W: 1.07 (0.97–1.18) M: 0.96 (0.88–1.04)	BMI: 30–34.9 W: 1.17 (1.07–1.29) M: 1.24 (1.14–1.35)	BMI: 25–26.4 W: 1.00 (0.87–1.15) M: 0.89 (0.73–1.07)	BMI: 26.5–27.9 W: 1.12 (0.98–1.30) M: 1.05 (0.86–1.27)	BMI: 30–34.9 W: 1.25 (1.09–1.43) M: 1.48 (1.22–1.79)
Korean Cancer Prevention Study (9)	1,213,829	82,372	W: 49.4y M: 45y	12y	23.0 to 24.9	BMI: 25–26.4 W: 0.98 (0.94–1.03) M: 0.97 (0.94–1.00)	BMI: 26.5–27.9 W: 1.02 (0.97–1.08) M: 0.99 (0.95–1.03)	BMI: 30–31.9 W: 1.16 (1.06–1.28) M: 1.20 (1.08–1.34)	BMI: 25–26.4 W: 1.0 (0.9–1.0) M: 1.0 (0.9–1.1)	BMI: 26.5–27.9 W: 1.0 (1.0–1.1) M: 1.1 (1.0–1.2)	BMI: 30–31.9 W: 1.2 (1.1–1.3) M: 1.5 (1.3–1.9)

Ref=reference group, CI=confidence interval, BMI=body mass index, W=women, M=men, E.=East, S.=South;

* median